REMARKS/ARGUMENTS

The non-final Office Action of July 17, 2009, has been carefully reviewed and these remarks are responsive thereto. Claims 1-3, 5, 6, 9-11, 13-15, 17-19, 21-25, and 27-29 were pending. Claims 1-3, 5, 6, 9-11, 13-15, 17-19, 21-25, and 27-29 were rejected. This response addresses the rejection. Claims 1, 2 and 27 have been amended. Claims 4, 7-8, 12, 16, and 20 were previously cancelled. Claims 1-3, 5, 6, 9-11, 13-15, 17-19, 21-25, 27-29 remain pending. No new matter has been added to the application.

Priority

The Office Action acknowledged applicant's claim for foreign priority under 35 U.S.C. 119 (A)-(D) to the foreign application EPO 02014991.0, but deemed that the disclosure of the foreign application EPO 02014991.0 fails to provide adequate support or enablement for one or more claims of this application. The Office Action stated that the instant claims disclose a delivery system comprising the NCAM Ig loop domains I, II, and III, wherein the delivery system further comprises an integrase, wherein the integrase is from the phiC31 bacteriophage. The Office Action stated that the application EPO 02014991.0 does not provide support for the use of the NCAM Ig loop domains I, II, and III or for the use of any integrase. The Office Action stated that the foreign priority document only recites a transposase (such as Sleeping Beauty) and not an integrase, and that the foreign priority application does not mention the integrase from the phiC31 bacteriophage or the NCAM Ig loop domains I, II, and III.

Applicant disagrees with the priority determination expressed in the Office Action. EPO 02014991.0 does indeed provide support for the use of the NCAM Ig loop domains I, II, and III (See page 1, line 27 through page 2, line 4 of EPO 02014991.0), as well as the use of an integrase (See page 2, line 32 through page 3, line 22 of EPO 02014991.0). Specifically, for NCAM, the specification of EPO 02014991.0 states "a cell adhesion molecule or a fragment thereof wherein cell adhesion molecule is selected from the group consisting of ... NCAM (neural cell adhesion molecule)...." (See page 1, lines 32-35). The immunoglobulin (Ig) loop domains I, II, and III in the current specification constitute a fragment of the NCAM cell

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adhesion molecule. Moreover, with respect to the use of integrase, the specification of EPO 02014991.0 states that the expression construct may be intended for chromosomal integration. (See page 3, lines 12-13). A preferred embodiment of the invention uses transposase, a member of the Rnase superfamily of proteins, which also includes retroviral integrases. One of ordinary skill in the art would recognize that an expression construct encoding for an integrase is similar to that of a transposase in that the expression construct would be intended for chromosomal integration. Thus, support is present in the specification of the foreign priority document for the Ig loop domains of NCAM because they are a fragment of NCAM, and support is present for an expression vector containing integrase, because it is intended for chromosomal integration. Therefore, the priority date of the present application is at least July 10, 2002, the date of filing of EPO 02014991.0.

Information Disclosure Statement

As previously noted, an English translation of the reference DE 100 56 136 from the Information Disclosure Statement filed 1/10/2005 is U.S. Patent Publication No. 2004/0191303. The reference DE 100 56 136 was cited in the International Search Report for the corresponding PCT/CH03/00453, which claims priority to EPO 02014991.0, which this application also claims priority to. The International Search Report was provided to the Office at the time of National Phase filing of the present U.S. application. The cover sheet of U.S. Patent Publication No. 2004/0191303 shows at item 30 that it corresponds to DE 100 56 136. Thus, Applicant respectfully requests that the Office make record that DE 100 56 136 has been considered in the present application.

Claim Rejections Under 35 U.S.C. §112

Claims 1-3, 5, 6, 9, 10, 13, 14, 17, 18, 21, and 27 were objected to under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. Specifically, the term "a DNA integrase activity" was considered to be new matter.

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Applicant respectfully disagrees with this rejection. The DNA integrase activity disclosed in the application is DNA integrase activity encoding a protein, not necessarily being a protein. While the Applicant disagrees with the basis of the pending rejection, Applicant has elected to amend claim 1 solely in an effort to expedite prosecution and without acquiescing to the propriety of the rejection. The language of the claim now recites "said delivery system comprises a molecule encoding a chromosomal integration activity." This amendment does not constitute new matter and is fully supported by the language of the specification. (See EPO 02014991.0 at page 3). Thus, the rejection should be withdrawn.

Claim Rejections Under 35 U.S.C. §103(a)

Claims 1-3, 5, 6, 22, 23, and 27 were rejected under 35 U.S.C. 103(a), as being unpatentable over Poulsen et al. (PGPUB 2005/0037445), in view of each Maurer et al. (Expert Opinion Biol Ther, 2001, 1:923-947), Groth et al. (Proc. Natl. Acad. Sci. USA, 2000, 97:5995-6000), Schreier et al. (J. Biological Chemistry, 1994, 269:9090-9098), and Ranheim et al. (Proc. Natl. Acad. Sci. USA, 1996: 93:4071-4075).

Claims 1-3, 5, 6, 9, 10, 13, 14, 17, 18, 21-23, and 27 were rejected under 35 U.S.C. 103(a), as being unpatentable over Poulsen et al., taken with each Maurer et al., Groth et al., Schreier et al., and Ranheim et al., in further view of each Sato et al. (J. Drug Target., 2001, 9:201-207) and Gosselin et al. (Bioconjugate Chem., 2001, 12:989-994).

Claims 1-3, 5, 6, 22-25, and 27 were rejected under 35 U.S.C. 103(a), as being unpatentable over Poulsen et al., taken with each Maurer et al., Groth et al., Schreier et al., and Ranheim et al., in further view of Li et al. (Acta Anaesthesiol. Sin., 2000, 38: 207-215, Abstract).

Claim 29 was rejected under 35 U.S.C. 103(a), as being unpatentable over Poulsen et al., in view of each Maurer et al., Smith et al. (U.S. Patent No. 6,329,501), and Charlton et al. (Developmental Biology, 2000, 221: 112-119).

Claims 11, 15, 19, and 29 were rejected under 35 U.S.C. 103(a) as being unpatentable over Poulsen et al., in view of each Maurer et al., Smith et al., and Charlton et al., in further view of both Sato et al. and Gosselin et al.

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Claims 1, 2, 5, 6, 27, and 28 were rejected under 35 U.S.C. 103(a), as being unpatentable over Murphy (U.S. Patent No. 6,635,476), in view of each Poulsen et al., Ranheim et al., and Groth et al.

Rejections based on Poulsen as the primary reference

Poulsen discloses targeting complexes that are capable of being internalized into cells. The targeting complexes in Poulsen are polycations. The polycations taught in Poulsen provide a binding agent to associate with a cell surface molecule. (See paragraphs [0079] and [0087] of Poulsen). As recognized in the Office Action, Poulsen does not specifically teach liposomes comprising DNA as a bridge between a nucleic acid and a targeting moiety. Thus, Poulsen does not teach liposomes comprising DNA in their internal compartment and having the cell adhesion molecule NCAM or a fragment thereof. Further, Poulsen is silent regarding targeting complexes that comprise "a molecule encoding a chromosomal integration activity" as claimed in claim 1.

The Office Action's proposed modification of Poulsen, i.e., substitute a liposome for the polycation in Poulsen, results in DNA somehow covalently linked to the liposome. The proposed modification of Poulsen does not result in DNA placed within an internal compartment of the liposome, as claimed in claim 1. Thus, even if the proposed combination of Poulsen and Maurer is deemed proper, it does not result in DNA placed within an internal compartment of the liposome, as claimed in claim 1.

Further, one of ordinary skill in the art at the time the invention was made would not have been motivated to modify Poulsen to provide liposomes which comprise in their internal compartment a pharmaceutical agent and which have linked to their external surface the cell adhesion molecule NCAM or a fragment thereof, wherein said pharmaceutical agent is DNA and said delivery system comprises a molecule encoding a chromosomal integration activity, as claimed in amended claim 1. As taught by Poulsen, polycations are different from liposomes in that "polycations have the ability to compact and neutralize the charge of the delivered DNA."

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(See paragraph [0004] of Poulsen). Poulsen uses polycationic agents to bind DNA resulting in a complex where the negative charge of the nucleic acid molecule is completely neutralized for internalization via normal receptor-mediated endocytosis. (See paragraph [0571] of Poulsen). Moreover, in Poulsen, the binding partner (i.e., NCAM) associates with a bioreactive species (i.e., DNA) via a nucleic acid binding agent (i.e., polycation) **covalently** linked to the binding partner. In Poulsen, the polycationic agent requires a source of negative charge on the nucleic acid for binding. (See paragraph [0573] of Poulsen). There is no teaching or suggestion in Poulsen to substitute a liposome for a polycation.

Indeed, Poulsen teaches away from using liposomes. Poulsen teaches that while non-viral vectors, such as liposomes and polycations, are less immunogenic, easier to produce, and do not need the safety considerations of viral vectors, liposomes and polycations have much lower transfection efficiency than viral vectors and also lack the cell specificity provided by viral vectors. (See paragraph [0004] of Poulsen). Poulsen teaches that a polycation has the unique ability to compact and neutralize the charge of delivered DNA. Poulsen teaches that modifying a polycation by placing it in a multi-component non-viral vector increases the transfection efficiency and cell specificity for therapeutic gene delivery. Poulsen does not teach how to avoid the problems of non-viral vectors by modifying liposomes. Nor does Poulsen teach how to attach NCAM or a fragment thereof via a transmembrane domain or a hydrophobic anchor molecule. Thus, one of ordinary skill in the art at the time of the present invention would not have been motivated to or have had a reasonable expectation of success to substitute the polycations required in Poulsen with liposomes.

None of the other cited references, i.e., Maurer, Groth, Schreier, Ranheim, Smith, Charlton, Sato, Gosselin, nor Li retract from Poulsen teaching that polycations must be used instead of liposomes. Also, Poulsen is silent as to the delivery system comprising an additional molecule encoding a chromosomal integration activity. None of the other references remedy the deficiencies of Poulsen with respect to liposomes comprising chromosomal integration activity. Maurer is directed to a review of liposomes for drug delivery and discusses only conventional drugs, DNA and pDNA (See Abstract and page 936, column 1 through page 941, column 1 of

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Maurer). Maurer is thus completely silent regarding using molecules to integrate DNA into a host genome. Groth is directed to integrase from phi31 to carry out site-specific integration in human cells, but is totally unrelated to NCAM and does not refer to liposomes. Schreier is directed to glycosylphosphatidylinositol-anchored proteins for use as targeting molecules for liposomes, and is entirely silent regarding chromosomal integration activity (See Abstract of Schreier). Ranheim is directed to the interaction of neural cell adhesion molecules (NCAM) on two different cells and is totally unrelated to chromosomal integration activity (See Abstract of Ranheim). Sato and Gosselin do not remedy the deficiencies in the other cited references as they do not disclose a chromosomal integration activity. Li also does not remedy the deficiencies because the Abstract, as recognized in the Office Action, generally refers to a liposomal method for delivering genes into the myocardium and is silent on having a chromosomal integration activity.

Consequently, it would not have been obvious for one of skill in the art to develop the invention of claim 1 merely from the disclosures of the references cited in the Office Action. Claim 1 is therefore patentable over Poulsen in view of any combination of Maurer, Groth, Schreier, Ranheim, Smith, Charlton, Sato, Gosselin, or Li. The pending dependent claims depend from claim 1 and are patentable for at least the same reasons as claim 1 is patentable and for the additional features recited therein.

Claim 29 is also patentable over the prior art. The Office Action concedes that Poulsen does not specifically teach liposomes as the bridge between the nucleic acid and the targeting moiety. The Office Action is incorrect to assume that, in light of Maurer, it would have been obvious to one of skill the art, at the time the invention was made, to modify the method of Poulsen et al. by substituting polycations with liposomes, with a reasonable expectation of success. As explained above, Poulsen actually teaches away from using liposomes as a leading delivery system of nucleic acids. While non-viral vectors are less efficient and specific than viral vectors, Poulsen only teaches that polycations, not liposomes, can be modified in a multi-component complex to overcome that limitation. Thus, one of ordinary skill in the art would not be motivated to combine the teaching of Maurer with Poulsen.

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The Office Action also acknowledges that neither Poulsen nor Maurer teach a transgene encoding the human dystrophin. While Smith et al. teaches the targeting of the dystrophin gene to muscles, it merely teaches that peptides, which target a gene for expression in muscles, can be used to target liposomes. As noted in the Office Action, Smith is silent on using NCAM or a fragment thereof linked to the external surface of the liposome or using lipsomes with a pharmaceutical agent contained in the internal compartment. While Charlton et al. teaches that muscle cells express NCAM on their surface, one of skill the art would not have modified Poulsen with the stated references to link NCAM to the external surface of a liposome to deliver the dystrophin gene to cells in view of Poulsen's teaching away from the use of liposomes in favor of polycations.

Sato et al. and Gosselin et al. do not remedy the deficiencies of the above mentioned references as they do not teach linking NCAM to the external surface of a liposome.

Rejection based on Murphy as the primary reference

Claims 1, 2, 5, 6, 27, and 28 were rejected under 35 U.S.C. 103(a), as being unpatentable over Murphy (U.S. Patent No. 6,635,476) in view of each Poulsen et al., Ranheim et al., and Groth et al. As discussed above, claim 1 includes the features that "said pharmaceutical agent is DNA and said delivery system comprises a molecule encoding a chromosomal integration activity." Murphy is directed to targeted vectors "that are complexed to a targeting moiety by coordinate covalent linkages mediated by a transition metal ion" (Abstract of Murphy). Murphy makes no mention of chromosomal integration activity and using fragments of NCAM. There is no teaching or suggestion in the prior art to modify Murphy and delete the required transition metal ion of Murphy. As noted above, Poulsen teaches away from using liposomes because of their limitations of low cell specificity and efficacy, and instead teaches use of polycations to covalently bond with DNA. One of ordinary skill in the art at the time of the present invention would not have looked to the polycation system of Poulsen to try to modify and improve the system of Murphy.

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Poulsen and Ranheim are discussed above as lacking disclosure related to liposomes comprising a chromosomal integration activity. Groth is directed to integrase from phi31 to carry out site-specific integration in human cells, but is totally unrelated to NCAM and liposomes. On of ordinary skill in the art would not have had a reasonable expectation of success at the time the present invention was made to combine integrase activity as taught by Groth with the teachings from Murphy and the other references. Moreover, none of the references teach linking a liposome via a transmembrane domain or a hydrophobic anchor molecule to NCAM, as the linkages taught in the references are covalent attachments.

Accordingly, claim 1 is patentable over Murphy in view of Poulsen and Ranheim. The dependent claims depend from claim 1 and are patentable for at least the same reasons as claim 1 and for the additional features recited therein.

The Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejections.

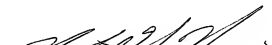
CONCLUSION

All rejections having been addressed, the Applicant respectfully submits that the instant application is in condition for allowance, and respectfully requests prompt notification of the same. If there are any questions, the Examiner is invited to contact Applicant's undersigned representative at the number noted below.

Respectfully submitted,

BANNER & WITCOFF, LTD.

Dated: November 17, 2009

By: 

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